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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/718,077	11/20/2003	Dave Dickason	CP185B	8643

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EXAMINER	
KAROL, JODY LYNN	
ART UNIT	**PAPER NUMBER**
1617	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/718,077	DICKASON ET AL.	
	Examiner	Art Unit	
	Jody L. Karol	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 December 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3 and 6-46* is/are pending in the application.

4a) Of the above claim(s) *22-46* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3 and 6-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This office action is in response to the Amendments and Remarks filed on 12/7/2007. Claims 1 has been amended, and claims 4-5 have been cancelled. Claims 1-3 and 6-46 are currently pending, and claims 21-46 remain withdrawn as corresponding to the non-elected invention. Accordingly, claims 1-3 and 6-21 are examined on the merits herein.

Status of Rejections/Objections

1. The rejection of claims 4-5 under 35 U.S.C. 103(a) as being unpatentable over Murakata et al. (WO 88/07045) in view of Matthews et al. (WO 00/48571) is herein withdrawn in view of Applicants' cancellation of these claims.

2. Applicants' arguments with respect to the rejection of claims 1-3 and 6-21 under 35 U.S.C. 103(a) as being unpatentable over Murakata et al. (WO 88/07045) in view of Matthews et al. (WO 00/48571) have been fully considered but are not found persuasive. Thus, the rejection is maintained and reproduced below.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

4. Claims 1-3 and 6-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Murakata et al. (WO 88/07045) in view of Matthews et al. (WO 00/48571).

Murakata et al. teach, in the abstract, derivatives of k-252 represented by formula I useful in formulating compositions having protein kinase C inhibiting activity. On page 43, Murakata et al. disclose that compounds of formula I can be administered as oleophilic and hydrophilic salts and can be dissolved in solution for administration in a

dose of 0.01-20 mg/kg. Oral and rectal administration are also contemplated. Compound 20 in Table 2 (pages 45-46) discloses the currently claimed species.

Murakata et al. does not teach the compound in at least 20% (w/w) of a polyoxyl stearate; and at least one polyethylene glycol; or the particular concentration as claimed, or polyethylene glycol having a particular weight; or the use of Myrj52; or the various ratios of the polyethylene glycol:polyoxyl stearate, etc.

Matthews et al. teach, in the abstract, spontaneously dispersible N-benzoyl-staurosporine compositions (a closely related compound to the one presently claimed), for oral administration having high bioavailability. On page 4, Matthews et al. teach that the N-benzoyl-staurosporine (active agent) can be present up to 20% by weight of the composition, can have a hydrophilic component and a surfactant and that the hydrophilic component can be lower alkanol components such as polyethylene glycols of 100-600 Daltons. The total amount of the hydrophilic component is 5-50% by weight. On pages 5-7, Matthews disclose that the pharmaceutical compositions comprise at least one surfactant that includes polyoxyethylene fatty acid esters, such as polyoxyethylene stearic acid esters sold under the trade name MYRJ. MYRJ 52 being particularly preferred. Other commercially available surfactants include Solutol HS15 and MEF 151E. These contain polyethoxylated hydroxystearate and polyethylene glycol mixtures.

Matthews et al. teach, on page 13, that the pharmaceutical compositions disclosed exhibit higher levels of oral bioavailability compared to previous compositions.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the compounds of Murakata et al. in the pharmaceutical compositions of Matthews et al. as the compounds disclosed in both are structurally related and have the same biological target of protein kinase C inhibition. One would be motivated to use the Matthews et al. formulation in order to take advantage of the increased oral bioavailability disclosed.

One of ordinary skill in the art would have been motivated to adjust the ratios of fatty acid esters and polyethylene oxide in order to maximize the formulations bioavailability.

The examiner respectfully points out the following from MPEP 2144.05: "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In *re Aller,* 220 F.2d 454,456, 105 USPQ 233,235 (CCPA 1955); see also Peterson, 315 F.3d at 1330, 65 USPQ2d at 1382 ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages."); *In re Hoeschele,* 406 F.2d 1403, 160 USPQ 809 (CCPA 1969); Merck & Co. Inc. v. Biocraft Laboratories Inc., 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989); *In re Kulling,* 897 F.2d 1147, 14 USPQ2d 1056 (Fed.Cir. 1990); and *In re Geisler,* 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997).

Response to Arguments

5. In response to the Applicants' argument that Murakata would not lead one of skill in the art to compositions comprising at least 20% by weight polyoxyl stearate and at least one polyethylene glycol in addition to the fused pyrrolocarbazole presented in claim 1 (i.e. lack of motivation provided by Murakata), the Examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In the instant case, motivation is provided by the Matthews et al. reference, teaching that spontaneously dispersible compositions comprising the fused pyrrolocarbazole: N-benzoyl-staurosporine, and hydrophilic component such as polyethylene glycol, and a surfactant such as Myrj© 52 (polyoxyl stearate), provide enhanced bioavailability. Thus, as previously stated on the record, the motivation to combine the references to provide the instant invention would be to provide a composition with enhanced bioavailability.

6. Applicants' arguments that Matthews' inclusion of a broad surfactant range indicates Matthews did not recognize the significance of the surfactant percentage to bioavailability, and that Matthews teaches away from the present of invention by listing alternative surfactants has been fully considered but not found persuasive. Applicants'

assert that polyoxyl stearate is required in the pharmaceutical compositions of the instant invention, and that this determination is unexpected.

However, it is applicant's burden to demonstrate unexpected results over the prior art. See MPEP 716.02, also 716.02 (a) - (g). Furthermore, the unexpected results should be demonstrated with evidence that the differences in results are in fact unexpected and unobvious and of both statistical and practical significance. *Ex parte Gelles*, 22 USPQ2d 1318, 1319 (Bd. Pat. App. & Inter. 1992). Moreover, evidence as to any unexpected benefits must be "clear and convincing" *In re Lohr*, 137 USPQ 548 (CCPA 1963), and be of a scope reasonably commensurate with the scope of the subject matter claimed, *In re Linder*, 173 USPQ 356 (CCPA 1972).

In the instant case, Applicants provides no evidence that polyoxyl stearate must be present in the composition comprising compound IIa-12, as recited in the instant claims. While the Examiner recognizes that the Applicants present exemplary compositions comprising IIa-12, a polyethylene glycol, and polyoxyl stearate (see page 40, line 1 to page 41 line 10 of the instant specification), other formulations comprising IIa-12 with different surfactants are presented in Table 2A for example (see page 42, Formulations (b) and (c)), and are indicated to have increased bioavailability of up to 300% (see page 43, lines 3-7).

Furthermore, the evidence present pertaining to the range of surfactant is not of a scope reasonably commensurate with the scope of the subject matter claimed. Only one example is provided in the instant specification that contains less than 20% by weight of a surfactant, SDS (see page 45, Table 4, Formulation D). However, this

composition does not contain polyethylene glycol, and thus does not provide sufficient evidence that the composition formulations of the instant invention containing less that 20% of polyoxyl stearate would demonstrate diminished bioavailability. Moreover, Matthews et al. clearly teach that compositions comprising from 5 to 80% by weight of a surfactant will increase bioavailability. Therefore, no clear and convincing unexpected benefit is seen to be present herein and the instant claims are still considered properly rejected under 35 USC 103(a).

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jody L. Karol whose telephone number is (571)270-3283. The examiner can normally be reached on 8:30 am - 5:00 pm Mon-Fri EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

JLK

/San-ming Hui/
Primary Examiner, Art Unit 1617